IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	**MAIL STOP APPEAL BRIEF - PATENTS**
Keiichirou Kai et al.	
Application No.: 10/578,912	Group Art Unit: 1623
Filed: May 9, 2006	Examiner: Layla D Bland
For: PROCESS FOR PRODUCING PENTOSE-5-PHOSPHATE ESTER	Appeal No.: _____

APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This appeal is from the decision of the Primary Examiner dated November 25, 2009 finally rejecting claims 1, 4, and 6, which are reproduced in the Claims Appendix of this brief.

☒ Charge ☐ $ 270 ☒ $ 540 to Credit Card.

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

I. Real Party in Interest

The present application is assigned to Mitsui Chemicals, Inc. Mitsui Chemicals, Inc. is the real party in interest, and is the assignee of Application No. 10/578,912.

II. Related Appeals and Interferences

The Appellant's legal representative, or assignee, does not know of any other appeal or interferences which will affect or be directly affected by or have bearing on the Board's decision in the pending appeal.

III. Status of Claims

Claims 1, 4, and 6 are pending in this application. Claims 2, 3, 5, 7, and 8 have been canceled. Claims 1, 4, and 6 have been finally rejected by the Office.

IV. Status of Amendments

No amendment was filed subsequent to final rejection.

V. Summary of Claimed Subject Matter

The claimed invention relates to the phosphorylation of pentose by an acid phosphatase. Specification, p. 2, lines 25-27. The reaction products are useful as starting materials for producing drugs and functional chemicals. *Id.*, p. 1, lines 10-12. The claimed process overcomes problems with the prior art including the requirements for numerous separation and purification steps, and the requirement for DNA or adenosine triphosphate as reactants, both of which are expensive. *Id.*, p. 1 at line 26 to p. 2 at line 7.

Claim 1 is the sole independent claim. It recites a process for producing a pentose-5-phosphate ester (p. 1, lines 7-9) wherein: a pentose is reacted with a phosphoric acid donor in the presence of an acid phosphatase (p. 3, lines 20-23); the

pentose is a pentose in (3S, 4R) or (3R, 4S) (p. 6, lines 5-7) and the pentose is ribose, arabinose or 2-deoxyribose (p. 2, lines 24-25); the pentose-5-phosphate ester is a pentose-5-phosphate ester in (3S, 4R) or (3R, 4S) and the pentose-5-phosphate ester is a ribose-5-phosphate ester, an arabinose-5-phosphate ester or a 2-deoxyribose-5-phosphate ester; the acid phosphatase is an acid phosphatase derived from *Shigella flexneri* (p. 7, lines 12); and the pentose is reacted with the phosphoric acid donor at a molar ratio of not less than 3 fold and not more than 7 fold phosphoric acid donor to pentose (p. 11, lines 9-12).

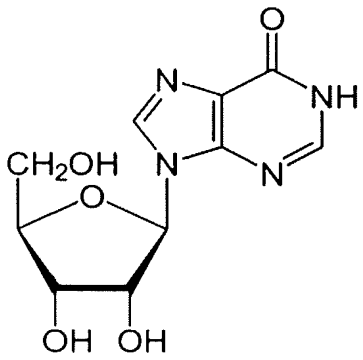
Figure 1 shows results when pentose is reacted with the phosphoric acid donor at varying molar ratios, both within (lines 2, 3, and 4) and outside (line 1) the scope of claim 1. Specification, p. 16, line 19 to p. 17, line 4.

VI. Grounds of Rejection to be Reviewed on Appeal

Claims 1, 4 and 6 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Tanaka et al., Org. Biomol. Chem., 2003, 1, 2833-2839, July 9, 2003 ("Tanaka") in view of Asano et al., Journal of Molecular Catalysis B: Enzymatic 7 (1999) 271-277 ("Asano") with evidence by Gross et al., J. Am. Chem. Soc. 1983, 105, 7428-7435 ("Gross").

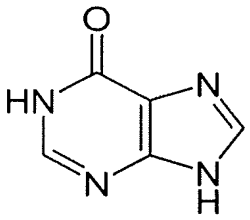
VII. Argument

Prior to the claimed invention, the acid phosphatase enzyme was known to phosphorylate inosine, the structure of which is reproduced below:

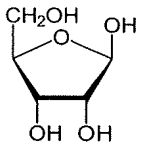


Inosine

Inosine can be considered to comprise two covalently joined substructures: hypoxanthine and ribose (which is a pentose).



Hypoxanthine



Ribose

The claimed process reacts acid phosphatase with certain types of pentose substrates that are not joined to hypoxanthine. Such pentose is sometimes termed "free pentose." Inosine is not one of the claimed substrates. Appellants submit that the evidence of record fails to support a contention that one of ordinary skill in the art would have predicted acid phosphatase to be effective to phosphorylate a free pentose such as ribose.

Biochemistry is an unpredictable art: one should not succumb to hindsight claims of obviousness merely because a researcher could try numerous possible choices until possibly arriving at a successful result, where the prior art gives no indication of which parameters are critical or no direction as to which of many possible choices is likely to succeed. *Proctor & Gamble Co. v. Teva Pharms. USA Inc.*, 90 USPQ2d 1947, 1951 (Fed. Cir. 2009) (citations omitted).

The rejection contends that, because Tanaka shows that glucose and inosine are viable substrates for acid phosphatase, one of ordinary skill in the art would purportedly expect free pentose to be a substrate for the enzyme as well. However, the references as applied contain nothing that would guide one of ordinary skill in the art towards using the claimed enzyme with the claimed substrates, as opposed to the countless numbers of other potential candidate substrates. Furthermore, the

record is full of evidence that the substrate specificity of the claimed enzyme cannot be predicted.

The primary reference itself notes that the claimed acid phosphatase derived from *Shigella flexneri* (termed therein "PhoN-Sf") has variable phosphatase activity depending on whether the inosine monophosphate is at the 5' position (5'IMP) or the 3' position (3'IMP). Tanaka, p. 2835, first column, second paragraph. Tanaka also reported that PhoN-Sf has "a much higher regioselectivity for the formation of 5'IMP." *Id.*, p. 2834, first column, last paragraph. Thus, even where two compounds have some apparent structural similarity, those two compounds are not necessarily effectively acted on by a common enzyme. Because substantial differences exist between the structures of inosine and pentose, the large difference in activity with 5'-IMP and 3'-IMP (which have nearly identical structures) would lead one of ordinary skill in the art away from considering the use of the enzyme with free pentose.

Tanaka describes additional unpredictable aspects of the claimed enzyme that would lead one of ordinary skill in the art away from a reasonable expectation that the enzyme would act on any particular untested substrate. For example, it states that the mechanism of glucose inhibition is complex and refers to such inhibition in providing "an interesting clue" to the enzyme function. *Id.*, p. 2837, first column, second paragraph. Tanaka also discusses the unpredicted variations in pyrophosphate ("PPi") activity between enzyme categories. *Id.*, p. 2838, first column, third paragraph. Tanaka fails to suggest that pentose could serve as a substrate for the enzyme.

Furthermore, data that Appellants have made of record further refutes the assumption of predictabley broad substrate specificity. Namely, the enzyme is quite selective even among particular pentoses: 2-deoxyribose, ribose, and arabinose were found to be phosphorylated, but D-xylose and D-lyxose were not. Evidence Appendix, p. 7. Similarly, among other substrates, the enzyme phosphorylated D-glucose, D- mannose, D-sorbitol, and D-glucosamine, but not D-galactose, D-myo-inositol and D-glucono-1,5-lactone. *Id.* at p. 10. The lack of pattern in the enzyme activity against various substrates further demonstrates the unpredictability of the field of art, and in particular the fact that one of ordinary skill in the art would not have a reasonable expectation of success in attempting to use the claimed enzyme to phosphorylate an untried substrate.

record is full of evidence that the substrate specificity of the claimed enzyme cannot be predicted.

The primary reference itself notes that the claimed acid phosphatase derived from *Shigella flexneri* (termed therein "PhoN-Sf") has variable phosphatase activity depending on whether the inosine monophosphate is at the 5' position (5'IMP) or the 3' position (3'IMP). Tanaka, p. 2835, first column, second paragraph. Tanaka also reported that PhoN-Sf has "a much higher regioselectivity for the formation of 5'IMP." *Id.*, p. 2834, first column, last paragraph. Thus, even where two compounds have some apparent structural similarity, those two compounds are not necessarily effectively acted on by a common enzyme. Because substantial differences exist between the structures of inosine and pentose, the large difference in activity with 5'-IMP and 3'-IMP (which have nearly identical structures) would lead one of ordinary skill in the art away from considering the use of the enzyme with free pentose.

Tanaka describes additional unpredictable aspects of the claimed enzyme that would lead one of ordinary skill in the art away from a reasonable expectation that the enzyme would act on any particular untested substrate. For example, it states that the mechanism of glucose inhibition is complex and refers to such inhibition in providing "an interesting clue" to the enzyme function. *Id.*, p. 2837, first column, second paragraph. Tanaka also discusses the unpredicted variations in pyrophosphate ("PPi") activity between enzyme categories. *Id.*, p. 2838, first column, third paragraph. Tanaka fails to suggest that pentose could serve as a substrate for the enzyme.

Furthermore, data that Appellants have made of record further refutes the assumption of predictably broad substrate specificity. Namely, the enzyme is quite selective even among particular pentoses: 2-deoxyribose, ribose, and arabinose were found to be phosphorylated, but D-xylose and D-lyxose were not. Evidence Appendix, p. 7. Similarly, among other substrates, the enzyme phosphorylated D-glucose, D- mannose, D-sorbitol, and D-glucosamine, but not D-galactose, D-myo-inositol and D-glucono-1,5-lactone. *Id.* at p. 10. The lack of pattern in the enzyme activity against various substrates further demonstrates the unpredictability of the field of art, and in particular the fact that one of ordinary skill in the art would not have a reasonable expectation of success in attempting to use the claimed enzyme to phosphorylate an untried substrate.

The original specification, viewed in conjunction with Tanaka, contains additional evidence leading one of ordinary skill in the art away from predicting that the claimed enzyme would act on the claimed substrates. As shown in Example 2 and FIG. 1 of the specification, deoxyribose is poorly phosphorylated under conditions similar to those used by Tanaka to obtain phosphorylation of glucose, *i.e.*, 100 mM substrate and 100 mM sodium pyrophosphate. Thus, although hexose and pentose both have hydroxyl groups and high polarity, a person of ordinary skill in the art would not have reasonably predicted that pentose, particularly the claimed ribose, arabinose and 2-deoxyribose, would be an effective substrate for acid phosphatase derived from *Shigella flexneri.*

The rejection relies on Asano to disclose phosphorylation using reagent concentrations within the claimed molar ratio, however Asano uses intact cells of *Morganella morgani* (Abstract), not the claimed acid phosphatase derived from *Shigella flexneri.* Asano fails to teach or suggest phosphorylation of pentose by an acid phosphatase as claimed, and thus does not cure the above-noted deficiencies of Tanaka.

The rejection relies on Gross to disclose the desirability of preparing ribose 5-phosphate (r-5-P). However, Gross prepares r-5-P using chemical methods including acid catalysis of either nucleotides or adenosine monophosphate, or using the enzyme ribokinase. These methods have nothing to do with the claimed phosphorylation of pentose by an acid phosphatase. Accordingly, Gross also fails to cure the above-noted deficiencies of Tanaka.

The references as applied give no indication to one of ordinary skill in the art that the claimed acid phosphatase might be employed to phosphorylate a pentose of ribose, arabinose or 2-deoxyribose to produce a 5-phosphate ester thereof, as claimed. Accordingly, Appellants submit that no legally-sufficient case of obviousness has been made out, and respectfully request reversal of the rejection.

VIII. Claims Appendix

See attached Claims Appendix for a copy of the claims involved in the appeal.

IX. Evidence Appendix

The Evidence Appendix contains the following, which was entered in the record on December 8, 2008: a Declaration Under 37 C.F.R. § 1.132 ("Kai Declaration"), reproduced as pages 2-10 of the Evidence Appendix.

X. Related Proceedings Appendix

As stated in the attached Related Proceedings Appendix, Appellant's legal representative, or assignee, does not know of any other appeal or interferences which will affect or be directly affected by or have bearing on the Board's decision in the pending appeal.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date May 18, 2010

By: _____
Roy Roberts
Registration No. 54402

Customer No. 21839
703 836 6620

Table of Contents

VIII. CLAIMS APPENDIX

The Appealed Claims

1. A process for producing a pentose-5-phosphate ester, wherein:

a pentose is reacted with a phosphoric acid donor in the presence of an acid phosphatase;

the pentose is a pentose in (3S, 4R) or (3R, 4S) and the pentose is ribose, arabinose or 2-deoxyribose;

the pentose-5-phosphate ester is a pentose-5-phosphate ester in (3S, 4R) or (3R, 4S) and the pentose-5-phosphate ester is a ribose-5-phosphate ester, an arabinose-5-phosphate ester or a 2-deoxyribose-5-phosphate ester;

the acid phosphatase is an acid phosphatase derived from *Shigella flexneri*; and

the pentose is reacted with the phosphoric acid donor at a molar ratio of not less than 3 fold and not more than 7 fold phosphoric acid donor to pentose.

4. The production process according to claim 1, wherein the phosphoric acid donor is a polyphosphoric acid or a salt thereof.

6. The production process according to claim 1, wherein the acid phosphatase is reacted under the condition that it is contained not less than 1 U/mL.

IX. EVIDENCE APPENDIX

The Evidence Appendix contains the following, which was entered in the record on December 8, 2008: a Declaration Under 37 C.F.R. § 1.132 ("Kai Declaration"), reproduced as pages 2-10 of the Evidence Appendix.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

---ooo:O:ooo---

In re Application of
Keiichirou KAI, et al.
Serial No. 10/578,912
Filed: May 9, 2006
For: PROCESS FOR PRODUCING PENTOSE-5-PHOSPHATE ESTER

Group Art Unit: 1623
Examiner: Keiichirou KAI

Honorable Commissioner of Patents and Trademarks
United States Patent and Trademark Office
Washington, D. C. 20231

Sir:

DECLARATION UNDER 37 CFR 1.132

I, Keiichirou KAI, declare and state that:

1. In March 1998, I was graduated from Kyusyu University, Agricultural Chemistry, Agricultural Division. In March 2000, I finished Master Course in Applied Microbiology, Faculty of Molecular Biotechnology in the same University.

Since April 2000, I have been an employee of MITSUI Petrochemical Industries Ltd., which has been named MITSUI Chemicals, Inc. Until March 2003, I had been assigned to Life Science Laboratory and engaged in the research work concerning Biocatalysis. Since April 2003, I have been assigned to group for Biocatalysis and Bioprocess in the Catalysis Science

Laboratory and engaged in research work concerning Molecular Biotechnology.

I am a co-inventor of the invention described in the above-identified application, and have a full understanding of the present invention.

2. I carried out the following experiment in order to demonstrate that acid phosphatase has a substrate specificity.

Experiments and Results

I demonstrate an additional experiment data, Examples A and B. That is:

The target compounds generated by the following Examples A and B were analyzed by the high performance liquid chromatography (hereinafter referred to as HPLC). Conditions of the HPLC analysis are shown below.

Column: Shodex Asahipak NH2P-50 4E (Showa Denko K.K.)

Mobile phase: 50 mM Sodium dihydrogen phosphate

Detector: Differential refractometer

The target compounds were bought, the compounds were analyzed by HPLC, and the working curves respectively were made.

The concentration of phosphoric acid ester was calculated from the analysis result of HPLC in using the working curve.

《For the pentose》

About (1)2-deoxy-D-ribose, (3)D-ribose and (5)D-arabinose, the concentration of each phosphoric acid ester was calculated from the working curve of its the signpost goods respectively.

About (2)2-deoxy-L-ribose, the concentration of phosphoric acid ester was calculated from the working curve of (1)2-deoxy-D-ribose.

About (6)L-arabinose, the concentration of phosphoric acid ester was calculated from the working curve of (5)D-arabinose.

About (4)D-xylose and (7)D-lyxose, there was no standard good, and the peak was not seen. Therefore, each yield was 0.

《For the hexose》

About (1)D-glucose, (2)2-deoxy-D-glucose, (3)D-mannose, (5)D-sorbitol, and (7)D-glucosamine, the concentration of each phosphoric acid ester was calculated from the working curve of its the signpost goods.

About (4)D-galactose, (6)D-myo-inositol, and (8)D-glucono-1,5-lactone, there was no standard good, and the peak was not seen. Therefore, each yield was 0.

Example A

To a solution containing 100mM of acetate buffer (pH=3.5), 700mM of a mixed solution (pH3.5) of a pyrophosphoric acid and a potassium pyrophosphate, and 100mM of various pentoses was added a bacterial cell solution to 0.73U/mL (0.5mg wer bacterial cell / mL) using the culture bacterial cell prepared in Reference Example 1. The resulting mixture was reacted at 30℃. The reaction solution was analyzed by HPLC.

The results thereform were shown in Table.A.

Table.A

(1) 2-deoxy-D-ribose

Reaction time	2-deoxy-D-ribose-5-phosphate
1hr	0.73mM
3hr	2.94mM
6hr	6.45mM
12hr	10.43mM
24hr	9.64mM

(2) 2-deoxy-L-ribose

Reaction time	2-deoxy-L-ribose-5-phosphate
1hr	1.13mM
3hr	2.97mM
6hr	7.07mM
12hr	9.69mM
24hr	9.39mM

(3) D-ribose

Reaction time	D-ribose-5-phosphate
1hr	1.62mM
3hr	4.66mM
6hr	7.51mM
12hr	13.45mM
24hr	9.78mM

(4) D-xylose

Reaction time	D-xylose-5-phosphate
1hr	0mM
3hr	0mM
6hr	0mM
12hr	0mM
24hr	0mM

(5) D-arabinose

Reaction time	D-arabinose-5-phosphate
1hr	0.43mM
3hr	1.06mM
6hr	1.88mM
12hr	3.34mM
24hr	2.51mM

(6) L-arabinose

Reaction time	L-arabinose-5-phosphate
1hr	0.22mM
3hr	0.59mM

6hr	1.15mM
12hr	2.22mM
24hr	1.60mM

(7) D-lyxose

Reaction time	D-lyxose-5-phosphate
1hr	0mM
3hr	0mM
6hr	0mM
12hr	0mM
24hr	0mM

From the results of the above Examples A, 2-deoxyribose, D-ribose and arabinose can be phsphorylated, on the other hand D-xylose and D-lyxose can not be phospharylated from various pentoses.

Example B

To a solution containing 100mM of acetate buffer (pH=3.5), 200mM of a mixed solution (pH3.5) of a pyrophosphoric acid and a potassium pyrophosphate, and 100mM of various hexoses was added a bacterial cell solution to 0.73U/mL (0.5mg wer bacterial cell / mL) using the culture bacterial cell prepared in Reference Example 1. The resulting mixture was reacted at 30℃. The reaction solution was analyzed by HPLC. The results thereform were shown in Table.B.

Table.B

(1) D-glucose

Reaction time	D-glucose-6-phosphate
1hr	34.3mM
2hr	51.6mM
4hr	67.2mM
8hr	71.3mM
12hr	64.5mM

(2) 2-deoxy-D-glucose

Reaction time	2-deoxy-D-glucose-6-phosphate
1hr	40.0mM
2hr	53.8mM
4hr	56.1mM
8hr	21.5mM
12hr	1.5mM

(3) D-mannose

Reaction time	D-mannose-6-phosphate
1hr	9.0mM
2hr	14.8mM
4hr	26.2mM
8hr	10.7mM
12hr	1.1mM

(4) D-galactose

Reaction time	D-galactose-6-phosphate
1hr	0mM

2hr	0mM
4hr	0mM
8hr	0mM
12hr	0mM

(5) D-sorbitol

Reaction time	D-sorbitol-6-phosphate
1hr	8.3mM
2hr	14.6mM
4hr	23.5mM
8hr	13.9mM
12hr	7.1mM

(6) D-myo-inositol

Reaction time	D-myo-inositol-phosphate
1hr	0mM
2hr	0mM
4hr	0mM
6hr	0mM

(7) D-glucosamine

Reaction time	D-glucosamine-6-phosphate
1hr	33.1mM
2hr	48.2mM
4hr	63.7mM
8hr	69.1mM
12hr	63.5mM

(8) D-glucono-1,5-lactone

Reaction time	D-glucono-1,5-lactone-6-phosphate
1hr	0mM
2hr	0mM
4hr	0mM
8hr	0mM
12hr	0mM

From the results of the above Examples B, D-glucose, D-mannose, D-sorbitol and D-glucosamine can be phsphorylated, on the other hand D-galactose, D-myo-inositol and D-glucono-1,5-lactone cannot be phsphorylated from various hexoses.

The undersigned declares further that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

This day of November 12, 2008

Keiichirou KAI

X. RELATED PROCEEDINGS APPENDIX

The Appellant's legal representative, or assignee, does not know of any other appeal or interferences which will affect or be directly affected by or have bearing on the Board's decision in the pending appeal.